

examination in the U.S. Support for the amendment to page 4 comes from the specification, as originally filed, at pages 23-26. Support for the new drawing comes from the specification, as originally filed, at page 26. A new sequence listing is submitted to satisfy the requirements of 37 C.F.R. § 1.821 - 1.825. No new matter is added. Currently, claims 1-36, 41-58, and 60-67 are pending in this application, all but claims 1 and 28 having been withdrawn from consideration by the Examiner in the Office Action.

I. *Compliance with Sequence Listing Rules.*

The Office Action states that the present application does not comply with 37 C.F.R. § 1.821(d). The Office Action also advises Applicants to review the specification for compliance with the Sequence Rules. Applicants have reviewed the specification and amended it where necessary to make reference to Sequence Identifiers. In addition, a new sequence listing (computer readable and paper copy) in accordance with the Sequence Rules, is attached hereto. In view of the amendments to the specification and the new sequence listing, Applicants respectfully submit that this application satisfies all of the requirements of 37 C.F.R. § 1.821-1.825.

II. *Drawing.*

The Office Action states that the application improperly contains a figure within the body of the specification. By this Amendment, the figure on page 26 is deleted. Filed concurrently herewith is a Request for Approval of Drawing Change in which Applicants propose to add to

the application the figure, originally contained on page 26, as a formal drawing. Support for the drawing comes from the specification, as originally filed, at page 26. A brief description of the drawing is added by this Amendment, at page 4. Upon entry of the formal drawing into the application, Applicants request that it be reviewed by the Draftsman, and any deficiencies or informalities be brought to the attention of Applicants.

III. *Objections to the Specification.*

The Office Action objects to the Title of the Invention and the Abstract. While not acquiescing to these objections, solely in an effort to expedite allowance of this application, Applicants have amended the Title of the Invention is to remove "NOVEL" and the Abstract to reduce the number of paragraphs from two to one. In view of the above amendments, Applicants respectfully request reconsideration and withdrawal of the objections to the specification.

IV. *Rejection Under 35 U.S.C. 103(a).*

In the Office Action, claims 1 and 28 are rejected under 35 U.S.C. § 103(a) over Brange (U.S. Patent No. 5,597,796) in view of Markussen *et al.* (WO 92/00321) and Brange *et al.* (WO 89/10937). Applicants respectfully traverse this rejection and submit that the invention claimed in claims 1 and 28 would not have been obvious to one of ordinary skill in the art in view of the combination of cited references.

Brange teaches insulin analogs that remain in monomeric form in relatively concentrated compositions. *See, for example*, Brange, column 4, lines 19-23. The analogs are capable of

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

maintaining their monomeric state due to substitutions at defined residues within the A- and B-chains which render the insulin more negatively charged. Brange, column 4, lines 61-65; column 8, lines 7-12. Because of their increased negative charge, and thus their ability to remain in monomeric form at high concentrations, the analogs disclosed by Brange do not show a delayed onset of activity, which typically occurs with administration of human or porcine insulin supplied at a high concentration. Brange, column 4, lines 24-32. In formula III (column 8), Brange discloses amino acid residues of human insulin that can be modified to improve the speed with which the insulin analog acts. Brange indicates that B3 is a particularly good position for substitution with an amino acid carrying a negative charge at neutral pH. Brange, column 8, line 63 through column 9, line 5. Brange discloses, as exemplary insulin analogs, molecules having multiple substitutions. Column 9, lines 44-60, for example. Contrary to the assertion of the Office (at page 6, last line of the first paragraph of the Office Action), Brange discloses analogs with substitutions at both B3 and B29. *See*, column 9, line 55, where a GluB29,GluB3,GluB9 human insulin analog is disclosed. However, nowhere does Brange disclose or suggest that B3 should be substituted with any other residue except one having a negative charge at neutral pH.

The Office asserts that claims 1 and 28 are rendered obvious over Brange in view of Markussen *et al.* and Brange *et al.* More specifically, the Office asserts that Brange teaches insulin analogs with substitutions at B29, but not B3. The Office then asserts that this deficiency of Brange is overcome by combining Markussen *et al.* (for the teaching human insulin substituted at B1-B6 with a positively charged residue) with Brange. The Office states that motivation to combine the substitution of a negatively charged residue at B29 (Brange) with a

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
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substitution of a positively charged residue at B3 (Markussen *et al.*) comes from Brange *et al.*, which teaches that multiple substitutions in insulin are desirable. Office Action at page 6, second full paragraph.

However, the Office has improperly combined the cited references, and thus has failed to set forth a proper *prima facie* case of obviousness. In order to set forth a *prima facie* case of obviousness where multiple references are relied upon, there must be some teaching, motivation, or suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art to achieve the presently claimed invention. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In addition, when determining whether it would have been obvious to modify a reference, the reference must be considered in its entirety, including portions that might lead one of ordinary skill in the art away from the claimed invention under examination. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

In the rejection under 35 U.S.C. § 103(a), the Office asserts that Brange does not teach modification of B3 with Asp or Glu in conjunction with modification of B29. However, as mentioned above, in fact Brange does disclose such a combination of modifications, at column 9, line 55 (GluB29,GluB3,GluB9 human insulin) among the many insulin analogs disclosed between column 8, line 14 and column 9, line 60. Interestingly, although Brange discloses, and specifically exemplifies, that B3 can be substituted, the only substitutions that are contemplated are those where a negative residue is introduced. Column 8, line 63 through column 9, line 5.

The desire to have a negatively charged residue at B3 is entirely consistent with the disclosure of Brange, as a whole: that is, to provide insulin analogs with a greater negative charge than wild-type insulin. Accordingly, it would be inconsistent with the disclosure of Brange to introduce a positive charge at B3 because this would not result in a more negatively charged analog, but rather a more positively charged one. Such a result would be diametrically opposite of that intended by Brange. In other words, the disclosure of Brange at column 8, line 63 through column 9, line 5, taken in the context of Brange as a whole, teaches away from putting a positively charged residue at position B3.

Because the disclosure of Brange would have discouraged one of ordinary skill in the art from introducing a positively charged residue at position B3, there would have been no motivation to modify Brange as suggested by the Office. Thus, the Office has failed to set forth a *prima facie* case of obviousness. For at least this reason, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 28 under 35 U.S.C. § 103(a) over Brange in view of Markussen *et al.* and Brange *et al.*

V. *Conclusion.*

Applicants submit that this application is in condition for allowance, and such action is earnestly solicited. If the Examiner believes anything further is necessary to place this application in better form for allowance, she is invited to contact Applicants' undersigned

representative at the telephone number listed below. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.



By: _____

A handwritten signature in dark ink, appearing to read "Matthew T. Latimer", written over a horizontal line.

Matthew T. Latimer
Reg. No. 44,024

Date: December 2, 1999

Attachments:

Sequence Listing
Request for Approval of Drawing Changes